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FILE LAST UPDATED: 01 May 1997 (19970501/UP)

This file contains CAS Registry Numbers for easy and accurate substance identification. TIFF images of CA abstracts printed between 1907-1966 are available in the PAGE display formats.

=> s inhibit?(2W)(ribonuclease or RNAse)

- 0 INHIBIT?
- 0 RIBONUCLEASE
- 0 RNASE
- L1 0 INHIBIT? (2W) (RIBONUCLEASE OR RNASE)

1.2

0 RIBONUCLEASE

=> file caplus

COST IN U.S. DOLLARS

SINCE FILE TOTAL ENTRY SESSION 5.92 6.07

FULL ESTIMATED COST

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FILE COVERS 1967 - 1 Mar 1999 VOL 130 ISS 10 FILE LAST UPDATED: 1 Mar 1999 (19990301/ED)

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This file supports REG1stRY for direct browsing and searching of all substance data from the REGISTRY file. Enter HELP FIRST for more information.

=> s ribonuclease

L3 7493 RIBONUCLEASE

=> s inhbit?(2W)(ribonuclease or RNAse)

225 INHBIT?

7493 RIBONUCLEASE

26792 RNASE

L4 0 INHBIT?(2W)(RIBONUCLEASE OR RNASE)

=> s inhibit?(2W)(ribonuclease or RNASE)

1138104 INHIBIT?

7493 RIBONUCLEASE

26792 RNASE

L5 851 INHIBIT? (2W) (RIBONUCLEASE OR RNASE)

=> d L5 851

L5 ANSWER 851 OF 851 CAPLUS COPYRIGHT 1999 ACS

AN 1967:8319 CAPLUS

DN 66:8319

TI Ribonucleic acids of the endoplasmic reticulum of animal cells

AU Rodionova, N. P.; Shapot, V. S.

CS Acad. Med. Sci. U.S.S.R., Moscow, USSR

SO Biochim. Biophys. Acta (1966), 129(1), 206-9 CODEN: BBACAQ

DT Journal

LA English

=> s chelator or chelating

6580 CHELATOR

=> s L6 and L5

L7 5 L6 AND L5

=> d L7 1-5

- 1.7 ANSWER 1 OF 5 CAPLUS COPYRIGHT 1999 ACS
- AN 1995:970399 CAPLUS
- DN 124:25038
- TI Factors affecting flow cytometric detection of apoptotic nuclei by DNA analysis
- AU Elstein, Kenneth H.; Thomas, David J.; Zucker, Robert M.
- CS National Health and Environmental Effects Research Laboratory, U.S. Environmental Protection Agency, Research Triangle Park, NC, USA
- SO Cytometry (1995), Volume Date 1995, 21(2), 170-6 CODEN: CYTODQ; ISSN: 0196-4763
- DT Journal
- LA English
- L7 ANSWER 2 OF 5 CAPLUS COPYRIGHT 1999 ACS
- AN 1994:186872 CAPLUS
- DN 120:186872
- TI The catalytic properties of the reverse transcriptase of the lentivirus equine infectious anemia virus
- AU Rubinek, Tami; Loya, Shoshana; Shaharabany, Miriam; Hughes, Stephen H.; Clark, Patrick K.; Hizi, Amnon
- CS Sackler Sch. Med., Tel Aviv Univ., Israel
- SO Eur. J. Biochem. (1994), 219(3), 977-83 CODEN: EJBCAI; ISSN: 0014-2956
- DT Journal
- LA English
- L7 ANSWER 3 OF 5 CAPLUS COPYRIGHT 1999 ACS
- AN 1992:16803 CAPLUS
- DN 116:16803
- TI Aluminum interrupts the formation of alkaline-ribonuclease-inhibitor complex from bovine brain
- AU Cho, Sung Woo; Kim, Geum Yi
- CS Coll. Med., Univ. Ulsan, Seoul, 138-040, S. Korea
- SO Eur. J. Biochem. (1991), 202(1), 107-11 CODEN: EJBCAI; ISSN: 0014-2956
- DT Journal
- LA English
- L7 ANSWER 4 OF 5 CAPLUS COPYRIGHT 1999 ACS
- AN 1979:470753 CAPLUS
- DN 91:70753
- TI Reverse transcriptase-associated RNase H. III. Reverse transcriptase-associated ribonuclease H does not require zinc for catalysis
- AU Modak, Mukund J.; Srivastava, Arun
- CS Memorial Sloan-Kettering Cancer Cent., New York, NY, 10021, USA
- SO J. Biol. Chem. (1979), 254(11), 4756-9 CODEN: JBCHA3; ISSN: 0021-9258
- DT Journal
- LA English
- L7 ANSWER 5 OF 5 CAPLUS COPYRIGHT 1999 ACS
- AN 1971:9771 CAPLUS
- DN 74:9771
- TI Extracellular nuclease activity of Micrococcus sodonensis. III. Kinetic studies and control of production

```
Berry, Sheila A.; Campbell, James N.
ΑU
    Dep. Microbiol., Univ. Alberta, Edmonton, Alberta, Can.
CS
    Biochim. Biophys. Acta (1970), 220(2), 256-68
    CODEN: BBACAQ
DT
    Journal
    English
LA
=> file medline or caplus
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=> file medline, caplus
                                                  SINCE FILE
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COST IN U.S. DOLLARS
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FULL ESTIMATED COST
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=> s ribonuclease(W)inhibitor#
           470 RIBONUCLEASE (W) INHIBITOR#
L8
=> s EDTA and L8
             8 EDTA AND L8
L9
=> d L9 1-8
    ANSWER 1 OF 8 MEDLINE
1,9
    92037631
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AN
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DN.
    Aluminum interrupts the formation of alkaline-ribonuclease-
TТ
    inhibitor complex from bovine brain.
    Cho S W; Kim G Y
ΑU
    Department of Biochemistry, College of Medicine, University of Ulsan,
CS
    Seoul, Korea.
    EUROPEAN JOURNAL OF BIOCHEMISTRY, (1991 Nov 15) 202 (1) 107-11.
SO
    Journal code: EMZ. ISSN: 0014-2956.
CY
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    Journal; Article; (JOURNAL ARTICLE)
DT
LA
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    Priority Journals; Cancer Journals
FS
EM
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L9
    ANSWER 2 OF 8 MEDLINE
AN
    81026444
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    81026444
    Isolation of giant silk fibroin polysomes and fibroin mRNP particles
ΤI
using
     a novel ribonuclease inhibitor, hydroxystilbamidine.
    Lizardi P M
AU
NC
    GM-22865 (NIGMS)
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JOURNAL OF CELL BIOLOGY, (1980 Oct) 87 (1) 292-6.

SO

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Journal code: HMV. ISSN: 0021-9525.
    United States
CY
    Journal; Article; (JOURNAL ARTICLE)
DT
LΑ
    English
    Priority Journals
FS
    198102
EM
    ANSWER 3 OF 8 CAPLUS COPYRIGHT 1999 ACS
L9
    1998:129464 CAPLUS
AN
    128:202352
DN
    Endogenous ribonuclease inhibitors of mammals, cDNAs
ΤI
    encoding them, and their uses
    Chatterjee, Deb K.; Shandilya, Harini
IN
    Life Technologies, Inc., USA; Chatterjee, Deb K.; Shandilya, Harini
PA
    PCT Int. Appl., 78 pp.
SO
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LΑ
    English
FAN.CNT 1
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    WO 9806845 A1 19980219 WO 97-US14254 19970814
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    US 97-910731
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    WO 97-US14254
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    ANSWER 4 OF 8 CAPLUS COPYRIGHT 1999 ACS
L9
    1992:16803 CAPLUS
ΑN
    116:16803
DN
    Aluminum interrupts the formation of alkaline-ribonuclease-
ΤI
    inhibitor complex from bovine brain
    Cho, Sung Woo; Kim, Geum Yi
ΑU
    Coll. Med., Univ. Ulsan, Seoul, 138-040, S. Korea
CS
    Eur. J. Biochem. (1991), 202(1), 107-11
SO
    CODEN: EJBCAI; ISSN: 0014-2956
DT
    Journal
    English
LΑ
    ANSWER 5 OF 8 CAPLUS COPYRIGHT 1999 ACS
L9
    1991:242030 CAPLUS
ΑN
DN
    114:242030
    Molecular cloning and expression of human placental ribonuclease
TI
    inhibitor CDNA
    Lewis, Martin Kendall; Shultz, John William
IN
PΑ
    Promega Corp., USA
    PCT Int. Appl., 42 pp.
SO
    CODEN: PIXXD2
\mathtt{D}\mathbf{T}
    Patent
    English
LΑ
FAN.CNT 1
                   KIND DATE
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    WO 9012881
                    A1 19901101
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                                                         19900418
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AU 90-55377
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    AT 162853
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    US 90-510881
    WO 90-US2122
                     19900418
                     19920324
    US 92-856863
    ANSWER 6 OF 8 CAPLUS COPYRIGHT 1999 ACS
L9
    1981:510314 CAPLUS
ΑN
    95:110314
DN
ΤI
    Effect of human placental ribonuclease inhibitor in
    cell-free ribosomal RNA synthesis
ΑU
    Eichler, Duane C.; Tatar, Todd F.; Lasater, Linda S.
    Coll. Med., Univ. South Florida, Tampa, FL, 33612, USA
CS
    Biochem. Biophys. Res. Commun. (1981), 101(2), 396-403
SO
    CODEN: BBRCA9; ISSN: 0006-291X
DT
    Journal
    English
LΑ
    ANSWER 7 OF 8 CAPLUS COPYRIGHT 1999 ACS
L9
    1980:634445 CAPLUS
ΑN
DN
    93:234445
    Isolation of giant silk fibroin polysomes and fibroin mRNP particles
ΤI
using
    a novel ribonuclease inhibitor, hydroxystilbamidine
ΑU
    Lizardi, Paul M.
CS
    Dep. Cell Biol., Rockefeller Univ., NY, 10021, USA
SO
    J. Cell Biol. (1980), 87(1), 292-6
    CODEN: JCLBA3; ISSN: 0021-9525
DT
    Journal
    English
LΑ
    ANSWER 8 OF 8 CAPLUS COPYRIGHT 1999 ACS
L9
AN
    1967:496893 CAPLUS
DN
    67:96893
TΙ
    Purification of ribonuclease inhibitor from pig
    cerebral cortex
AU
    Takahashi, Yasuo; Mase, Keikichi; Suzuki, Y.
CS
    Niigata Univ. Sch. Med., Niigata, Japan
SO
    Experientia (1967), 23(7), 525-6
    CODEN: EXPEAM
DT
    Journal
    English
LΑ
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FILE 'USPAT' ENTERED AT 08:47:57 ON 01 MAR 1999

=> s hydroxyquinoline (P)phenol

3086 HYDROXYQUINOLINE 97043 PHENOL

L1 238 HYDROXYQUINOLINE (P) PHENOL

=> s RNA or DNA

17776 RNA 30040 DNA

L2 31193 RNA OR DNA

=> s L1 and L2

L3 58 L1 AND L2

=> d L3 1-58

- 1. 5,866,410, Feb. 2, 1999, Cloning of the biosynthetic pathway for chlortetracycline and tetracycline formation and cosmids useful therein; Michael J. Ryan, et al., 435/320.1 [IMAGE AVAILABLE]
- 2. 5,846,531, Dec. 8, 1998, Marine mela gene; Ronald M. Weiner, et al., 424/94.4; 435/189 [IMAGE AVAILABLE]
- 3. 5,837,505, Nov. 17, 1998, Melanin production from transformed escherichia coli; Guy della-Cioppa, et al., 435/128, 193, 244, 252.33; 536/23.2, 23.4 [IMAGE AVAILABLE]
- 4. 5,817,631, Oct. 6, 1998, Therapeutic uses of melanin; David L. Berliner, et al., 514/21; 424/94.4, 195.11; 514/64, 567 [IMAGE AVAILABLE]
- 5. 5,814,495, Sep. 29, 1998, Melanin production by streptomyces; Guy della-Cioppa, et al., 435/120; 424/60; 435/191, 252.35, 253.5 [IMAGE AVAILABLE]
- 6. 5,807,527, Sep. 15, 1998, Solid medium and method for **DNA** storage; Leigh Alexander Burgoyne, 435/5, 6, 7.1, 7.2, 7.9, 91.2; 536/24.3, 24.32, 24.33 [IMAGE AVAILABLE]
- 7. 5,776,968, Jul. 7, 1998, Therapeutic uses of melanin; David L. Berliner, et al., 514/414, 12, 415 [IMAGE AVAILABLE]
- 8. 5,756,126, May 26, 1998, Dry solid medium for storage and analysis of genetic material; Leigh Alexander Burgoyne, 424/488; 422/55, 56, 57; 435/4, 5, 6, 7.1, 7.2, 7.9, 91.2, 174, 183, 970 [IMAGE AVAILABLE]
- 9. 5,743,477, Apr. 28, 1998, Insecticidal proteins and method for plant

- protection; Terence A. Walsh, et al., 424/94.6; 435/198 [IMAGE AVAILABLE]
- 10. 5,703,051, Dec. 30, 1997, Therapeutic uses of melanin; David L Berliner, et al., 514/21; 424/94.4, 195.11; 514/63, 567 [IMAGE AVAILABLE]
- 11. 5,663,048, Sep. 2, 1997, Y-chromosome specific polynucleotide probes for prenatal sexing; Robert J. Winkfein, et al., 435/6, 91.2; 536/24.3 [IMAGE AVAILABLE]
- 12. 5,656,596, Aug. 12, 1997, Method of treating lesions in a nervous system; Denis Monard, et al., 514/12; 435/69.4; 514/2; 530/399; 536/23.5, 23.51; 930/120 [IMAGE AVAILABLE]
- 13. 5,631,151, May 20, 1997, Melanin production by transformed organisms; Guy della-Cioppa, et al., 435/133, 108, 189; 536/23.2 [IMAGE AVAILABLE]
- 14. 5,591,605, Jan. 7, 1997, Plant structural gene expression; Timothy C. Hall, et al., 800/294; 435/69.1, 320.1, 414, 415, 416, 419; 536/23.6, 24.1; 800/298, 300, 301, 302, 317, 317.3, 322 [IMAGE AVAILABLE]
- 15. 5,589,385, Dec. 31, 1996, Cloning of the biosynthetic pathway for chlortetracycline and tetracycline formation and cosmids useful therein; Michael J. Ryan, et al., 435/252.35, 252.31, 252.32, 252.33, 320.1; 536/23.2, 23.7 [IMAGE AVAILABLE]
- 16. 5,532,246, Jul. 2, 1996, Use of 1,3-oxathiolane nucleoside analogues in the treatment of hepatitis B; Bernard Belleau, deceased, et al., 514/274 [IMAGE AVAILABLE]
- 17. 5,529,909, Jun. 25, 1996, Tyrosinase-activator protein fusion enzyme; Guy della-Cioppa, et al., 435/69.7, 189, 252.3, 252.33, 252.35, 320.1; 536/23.2, 23.4 [IMAGE AVAILABLE]
- 18. 5,504,200, Apr. 2, 1996, Plant gene expression; Timothy C. Hall, et al., 800/298; 435/69.1, 70.1, 252.2, 252.3, 252.33, 320.1, 419; 536/23.6; 800/300, 301, 302, 317.3, 322 [IMAGE AVAILABLE]
- 19. 5,496,562, Mar. 5, 1996, Solid medium and method for **DNA** storage; Leigh A. Burgoyne, 424/488, 443, 464 [IMAGE AVAILABLE]
- 20. 5,486,520, Jan. 23, 1996, 1,3-oxathiolanes useful in the treatment of hepatitis; Bernard Belleau, deceased, et al., 514/274, 49 [IMAGE AVAILABLE]
- 21. 5,413,915, May 9, 1995, Method and sensor for detecting toxic chemical exposure effects and metabolic activation of carcinogenic chemical agents; George D. Case, et al., 435/25; 422/56; 435/287.9, 288.7, 317.1 [IMAGE AVAILABLE]
- 22. RE 34,875, Mar. 14, 1995, Method of selecting recombinant DNA-containing streptomyces; Virginia A. Birmingham, et al., 435/475, 252.3, 252.35, 320.1, 476, 486; 536/23.1, 23.2, 23.7 [IMAGE AVAILABLE]
- 23. 5,357,636, Oct. 25, 1994, Flexible protective medical gloves and methods for their use; Karl P. Dresdner, Jr., et al., 2/161.7, 167, 168, 169 [IMAGE AVAILABLE]
- 24. 5,310,678, May 10, 1994, Newcastle disease virus gene clones; Richard W. Bingham, et al., 435/252.3, 69.3, 235.1, 252.31, 252.33, 252.35, 254.11; 536/23.72 [IMAGE AVAILABLE]

- 25. 5,268,290, Dec. 7, 1993, Process for producing neuraminidase; Mamoru Hasegawa, et al., 435/201, 69.1, 200, 252.35, 320.1; 536/23.2 [IMAGE AVAILABLE]
- 26. 5,245,026, Sep. 14, 1993, Metal containing 8-hydroxyquinoline chelating agents; David K. Johnson, et al., 540/3, 470, 474; 546/2, 178, 180 [IMAGE AVAILABLE]
- 27. 5,233,044, Aug. 3, 1993, Active esters for solid phase peptide synthesis; Derek Hudson, 548/110, 368.1, 371.1 [IMAGE AVAILABLE]
- 28. 5,198,360, Mar. 30, 1993, **DNA** sequence conferring a plaque inhibition phenotype; Margaret M. Ballou, et al., 435/252.3, 252.35, 320.1; 536/23.72 [IMAGE AVAILABLE]
- 29. 5,187,080, Feb. 16, 1993, **DNA** encoding an antigenic protein derived from Eimeria tenella and vaccines for prevention of coccidiosis caused by Eimeria tenella; William H. Andrews, et al., 435/69.3; 424/191.1, 267.1; 435/69.1, 91.41, 235.1, 252.3, 252.33, 320.1; 530/300, 350, 388.6; 536/23.4, 23.7 [IMAGE AVAILABLE]
- 30. 5,165,925, Nov. 24, 1992, Vaccine for immunizing fish against infectious pancreatic necrosis virus; Jo-ann C. Leong, 424/186.1, 204.1, 817; 435/69.3; 536/23.72 [IMAGE AVAILABLE]
- 31. 5,130,250, Jul. 14, 1992, Molecular cloning and expression of neutral protease genes; Alan H. Deutch, et al., 435/252.33, 68.1, 91.41, 221, 320.1; 530/350; 536/23.2 [IMAGE AVAILABLE]
- 32. 5,102,796, Apr. 7, 1992, Plant structural gene expression; Timothy C. Hall, et al., 435/252.2, 252.3, 320.1; 536/23.2, 23.6, 23.7, 24.1 [IMAGE AVAILABLE]
- 33. 5,047,345, Sep. 10, 1991, Composition for isolating and purifying nucleic acid and improved method using same; David A. DeBonville, et al., 435/270, 6, 259, 803; 536/25.41, 25.42 [IMAGE AVAILABLE]
- 34. 5,039,667, Aug. 13, 1991, Antiviral therapy for hepatitis B with 2',3'-dideoxypurine nucleosides; David L. J. Tyrrell, et al., 514/45; 424/43, 433, 436, 464; 514/46; 536/27.14, 27.6, 27.61, 27.8, 27.81 [IMAGE AVAILABLE]
- 35. 5,032,520, Jul. 16, 1991, **DNA** sequences encoding infectious bronchitis virus spike protein; Matthew M. Binns, et al., 435/364, 69.1, 70.1, 91.41, 91.51, 235.1, 236, 320.1; 536/23.72, 24.1 [IMAGE AVAILABLE]
- 36. 5,032,501, Jul. 16, 1991, **DNA** probes to vntr loci; Eric C. B. Milner, 435/6; 536/24.3, 24.31 [IMAGE AVAILABLE]
- 37. 5,028,694, Jul. 2, 1991, Antigenic proteins and vaccines containing them for prevention of coccidiosis caused by eimeria Eimeria necatrix and Eimeria tenella; Karel Z. Mewman, Jr., et al., 530/350; 424/267.1; 530/388.6, 806, 825; 536/23.7 [IMAGE AVAILABLE]
- 38. 5,021,567, Jun. 4, 1991, 8-hydroxyquinoline chelating agents; David K. Johnson, et al., 540/470, 474; 546/169 [IMAGE AVAILABLE]
- 39. 4,983,525, Jan. 8, 1991, Plasmids derived from actinomadura species; Jerald S. Feitelson, et al., 435/320.1, 252.3, 825 [IMAGE AVAILABLE]

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(FILE 'USPAT' ENTERED AT 08:47:57 ON 01 MAR 1999)

L1 238 S HYDROXYQUINOLINE (P) PHENOL

L2 31193 S RNA OR DNA

L3 58 S L1 AND L2

=> d L3 52

52. 4,833,239, May 23, 1989, Method for the isolation and purification of **DNA** molecules; David A. DeBonville, et al., 536/25.41 [IMAGE AVAILABLE]

=> d ab

US PAT NO: 5,866,410 [IMAGE AVAILABLE] L3: 1 of 58

ABSTRACT:

The present invention describes a purified and isolated nucleic acid molecule which encodes for the biosynthetic pathway of tetracycline, chlortetracycline or an analogue thereof. The invention relates to the isolation and cloning of the nucleic acid molecule in an isolated fragment from Streptomyces aureofaciens and the expression of the biosynthetic gene in a heterologous host such as Streptomyces lividans.

=> d kwic

US PAT NO: 5,866,410 [IMAGE AVAILABLE] L3: 1 of 58

SUMMARY:

BSUM(4)

The . . . which can be protoplasted and regenerated. More importantly, protoplasts later proved to be an ideal substrate for transformation by plasmid **DNA**, thus creating the opportunity to do recombinant **DNA** experiments in these organisms (Bibb et al., 1978). The isolation of genes for several antibiotic resistances, such as thiostrepton, viomycin. . .

SUMMARY:

BSUM(7)

Another . . . for antibiotic biosynthesis were physically linked to the resistance determinant(s) for that same antibiotic in the producing organism. Thus, a DNA fragment from Streptomyces ariseus conferring streptomycin resistance was shown to be contiguous with DNA that complemented biosynthetic blocks (Distler et al., 1985). The same situation was seen in Streptomyces fradiae where biosynthetic genes had been identified by probing a cosmid library for homology to a mixed-base oligonucleotide constructed to represent the DNA sequence for the amino-terminus of the final enzyme in the tylosin biosynthetic pathway (Fishman et al., 1989). A previously cloned tylosin resistance gene (tlrB) was shown to be contained within this region of DNA, which complemented nine classes of blocked mutants (Baltz et al., 1988). In the cases of puromycin (Vara et al., 1988). . . resistance gene in the heterologous host Streptomyces lividans allowed subsequent identification of antibiotic biosynthetic genes located on the same cloned DNA fragment.

SUMMARY:

BSUM(8)

The . . . by hybridization to both a previously cloned resistance determinant (Butler et al., 1989) and an oligonucleotide synthesized to represent the **DNA** sequence corresponding to the partially elucidated amino acid sequence of the biosynthetic enzyme anhydrotetracycline oxygenase (Binnie et al., 1989). The. . .

SUMMARY:

BSUM(11)

Two . . . in the same S. lividans host, tetracenomycin was produced. Bifunctional clones isolated from an E. coli library of Streptomyces peucetius DNA by hybridization to actI and actIII probes of S. coelicolor were shown to direct the synthesis of pigmented antibiotic when. . .

SUMMARY:

BSUM(14)

The present invention is the first instance wherein the single **DNA** gene cluster related to the entire biosynthetic pathway for producing tetracycline and chlortetracycline is isolated and utilized.

DRAWING DESC:

DRWD(4)

FIG. . . . 3. The vector portion is represented by double line. The TC/CTC biosynthetic region is shown as a single line. The DNA cloned from S. aureofaciens is 31.9 kb; the vector is 11.1 kb. The vector regions denoted are pIBI-24 (hatched), thiostrepton-resistance. . . two EcoRI sites marked with a (+) are vector-derived and flank the Sau3A-BqlII junction which demarcates vector and S. aureofaciens DNA.

DRAWING DESC:

DRWD (5)

FIG. 3 shows the restriction endonuclease map for S. aureofaciens DNA which is cloned in LP.sup.2 127 and LP.sup.2 128. The 31.9 kb of DNA cloned in LP.sup.2 127 and LP.sup.2 128 is shown in linear form. The map is drawn so as to include. . .

DRAWING DESC:

DRWD(6)

FIGS. 4A-4L show the total DNA sequence from the cosmid clones designated LP.sup.2 127 and LP.sup.2 128 (this sequence is also set forth in Sequence I.D.. . . obtained using the dideoxy chain termination method (Sanger et al., Proc. Natl. Acad. Sci. USA, 74:5463-5467, 1977). The S. aureofaciens DNA carried in the cosmid clones is fragmented either by digestion with appropriate restriction endonuclease or by sonication. The smaller pieces. . . et al., Molecular Cloning: A Laboratory Manual, 2d ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1989). The DNA sequencing is carried out at elevated temperatures using Tag DNA polymerase employing fluorescently-labeled primers using materials and methods supplied by the manufacturer (Applied Biosystems, Foster City, Calif.). The data are collected using a Model 370A/373A DNA sequencing system (Applied Biosystems, Foster City, Calif.). Compilation of the data, generation of overlapping sequences and the overall analysis of this DNA sequence information are carried out using the collection of standard computer programs contained within the Genetics Computer Group package (Devereaux.

DETDESC:

DETD(2)

The . . . host such as Streptomyces lividans. In particular, the present invention concerns the purified and isolated nucleic acid molecule, e.g., a **DNA** gene cluster, coding for the biosynthetic pathway for producing the antibiotics or an analogue thereof.

DETDESC:

DETD(5)

In . . . The nucleotide sequence of the nucleic acid molecule is shown in FIG. 4. Desirably, the nucleic acid molecule is a **DNA** gene cluster isolated from Streptomyces aureofaciens, or an antibiotic-producing mutant thereof, and expressed in a suitable heterologous host, such as. . .

DETDESC:

DETD(6)

The present invention further includes the **DNA** sequences which hybridize under standard or stringent conditions to the sequence of the nucleic acid molecule isolated from the microbial. . .

DETDESC:

DETD(7)

Additionally, . . . Together, the plasmids comprise an efficient cosmid vector which allows for the cloning and packaging of large, contiguous pieces of **DNA**. It is contemplated that these plasmids described herein may be employed for cloning large **DNA** from any source.

DETDESC:

DETD(8)

For . . . biosynthetic genes, a screen of a recombinant S. lividans library for a clone expressing tetracycline-resistance is utilized. The S. aureofaciens DNA inserts in the recombinant cosmids which comprise the library are large since the constraints of the in vitro lambda packaging system demands cosmid molecules with DNA inserts of 25-40 Kb to yield a viable transducing phage particle. When tetracycline resistant clones are selected from among this. . .

DETDESC:

DETD(9)

The method for isolating the **DNA** involves lysozyme digestion of cells in an osmotic buffer, followed by gentle lysis, protein extraction and enrichment for, and concentration of, high molecular weight **DNA**. Although the method described is efficient, those skilled in the art will recognize that a variety of alternative procedures may. . .

DETDESC:

DETD(10)

The source of total ${\tt DNA}$ used in the examples is Streptomyces aureofaciens ATCC 13899 but the invention is not limited to this particular source. A. . .

DETDESC:

DETD(11)

A partial digestion of S. aureofaciens DNA with restriction endonuclease Sau3A to generate large DNA fragments in the desired 35-kilobase size range with ends homologous to those of the arms of the bifunctional cosmid vector. . . products by agarose gel electrophoresis. Those skilled in the art will recognize alternative library construction and recovery methods for cloned DNA of interest. The present invention is not limited to the use of Escherichia coli and the size selection imposed by. . .

DETDESC:

DETD(12)

The steps that follow in the examples involve in vitro packaging of the ligation products of cosmid arms and size fractionated DNA, transduction to E. coli X2819T, collection of the population of transductants and isolation of DNA from them to give a cosmid library. The methods used are described, but the invention is not limited by those. . .

DETDESC:

DETD(13)

Subsequent steps in the examples describe introduction of the pooled cosmid **DNA** preparation into Streptomvces lividans, creation of a cell library and subsequent screening of such a library for transformants of S....

DETDESC:

DETD (14)

Next, recovery of recombinant plasmid by isolating plasmid DNA from the tetracycline-resistant S. lividans followed by in vitro packaging of said DNA and transduction into E. coli is obtained. Plasmid DNA isolated from such transductants is structurally characterized by restriction enzyme mapping analysis; and the two plasmids isolated in the example, . . . LP.sup.2 127 and LP.sup.2 128, are shown to possess equivalent structures. Those skilled in the art will recognize that similar DNA regions cloned from alternative organisms could show polymorphism in the arrangement of restriction sites, but that a sufficiently large DNA fragment conferring tetracycline-resistance would be expected to confer the properties described hereinbelow.

DETDESC:

DETD(16)

Finally, . . . LP.sup.2 127 transformant of S. lividans produce tetracycline and chlortetracycline under conditions where the same products are isolated from the **DNA** source organism Streptomyces aureofaciens ATCC 13899. On the other hand, a S. lividans transformant containing only plasmid vector with no inserted **DNA** shows no antibiotic production.

DETDESC:

DETD (19)

PREPARATION OF STREPTOMYCES AUREOFACIENS TOTAL DNA

DETDESC:

DETD(22)

Once lysis is complete, 20 mL of equilibrated phenol (50 g phenol+6.5 mL of 100 mM NaCl, 10 mM Tris pH8, 1 mM EDTA pH8+0.05 g 8-hydroxyquinoline) is added, the preparation gently shaken and then spun in a table top centrifuge at 1500 .times.g for 30 minutes. The aqueous top layer is collected and re-extracted as above; the spent phenol from the first extraction is back-extracted with 20 mL 10 mM Tris pH7.4, 1 mM EDTA pH 8 (TE). The. . . pH 5 is added to each and 10 mL of cold ethanol layered on top of the viscous solution. The DNA is gently spooled onto a glass rod, rinsed twice in cold ethanol and dissolved in 8 mL TE overnight at 4.degree. C. An A.sub.260 spectrophotometric reading is taken as an estimate of total nucleic acids present (predominantly DNA).

DETDESC:

DETD(24)

PARTIAL DIGESTION AND SIZE ENRICHMENT OF S. AUREOFACIENS DNA

DETDESC:

DETD(25)

A partial digestion condition that yields Sau3A digestion products of S. aureofaciens DNA in the range of 35 kilobases (Kb) is determined empirically. A series of reaction tubes containing .about.25 .mu.q DNA contained in 300 .mu.L of reaction buffer consisting of 100 mM NaCl, 10 mM Tris pH7.4 10 mM MgCl.sub.2 are. . . and restriction endonuclease Sau3A (New England Biolabs) added to give final concentrations of 0.5, 0.1, 0.05, 0.01, 0.005 enzyme units/.mu.g DNA. The reactions are incubated at 37.degree. C. for 60 minutes, then placed at 65.degree. C. for 20 minutes and finally. . . ice. Twenty .mu.L is removed and loaded to 0.5% agarose gel for size comparison to fragments of known length (lambda DNA digested with HindIII, XhoI and undigested). The DNA in the remaining volume is precipitated by the sequential additions of 50 .mu.L 3M ammonium acetate and 1 mL ethanol, followed by chilling at -20.degree. C. The precipitated DNA is then pelleted by centrifugation at 8800 .times.g, redissolved in 300 .mu.L 0.3M ammonium acetate, similarly precipitated, pelleted, rinsed with. the ethidum bromide stained agarose gel which is electrophoresed overnight at 1 volt/cm, reveals that digestion with 0.05 units Sau3A/.mu.g DNA gives digestion products largely in the desired 35 Kb size range.

DETDESC:

DETD(29)

Plasmid A is digested with Asp718 and then desphosphorylated with calf intestine alkaline phosphatase (CIAP). The **DNA** then is extracted with chlorpane and chloroform, precipitated with ethanol and vacuum dried. The **DNA** is then resuspended and digested with BglII. Plasmid B is digested with SalI and subsequently treated with CIAP. After chlorpane extraction, ethanol precipitation and vacuum drying, the **DNA** is resuspended and digested with BglII.

DETDESC:

DETD(33)

LIGATION OF COSMID ARMS TO SAU3A DIGESTED GENOMIC **DNA** AND IN VITRO PACKAGING

DETDESC:

DETD(34)

The Sau3A digested and size "inspected" genomic fragments of S. aureofaciens DNA are joined to cosmid arms via in vitro ligation. Four .mu.L Sau3A digested S. aureofaciens DNA, corresponding to .about.8 .mu.g, are combined with 1 .mu.g each of cosmid arms 1 and 2 in a 10 .mu.L . . . 66 mM Tris pH7.4, 10 mM MgCl.sub.2, 1 mM ATP, 10 mM dithiothreitol and 40 units (cohesive end unit) T4 DNA ligase (New England Biolabs). The ligation mixture is incubated at 11.degree. C. for 18 hours then subjected to an in vitro packaging reaction by adding the entire 10 .mu.L reaction to a Packagene.sup.R lambda DNA packaging system extract (Promega Biotec). After a 2 hour incubation at room

temperature, 500 .mu.L phage dilution buffer (PDB) (100. . .

DETDESC:

DETD (37)

The . . . transduced into Escherichia coli X2819T (R. Curtiss), with the objective of obtaining thousands of transductants from which a pooled plasmid DNA preparation, or bifunctional cosmid library, can be obtained. To this end, 0.3 mL of an overnight culture of X2819T is. . .

DETDESC:

DETD (38)

Each . . . The aqueous solution is brought to 6 mL with TE; 1 mL 3M ammonium acetate is added and the plasmid **DNA** precipitated with 18 mL of ethanol. After chilling at -20.degree. C. the **DNA** is pelleted by centrifugation at 3400 .times.g for 30 minutes. A second precipitation is similarly performed, then the **DNA** is rinsed with ethanol, vacuum dired, dissolved in 1 mL TE and the **DNA** concentration is determined spectrophotometrically.

DETDESC:

DETD (41)

The . . . spinning at 3400 .times.g for 10 minutes and then resuspended in the residual volume. Approximately 10 .mu.g of cosmid library DNA is added to each, followed by the addition of 0.5 ML of 25% PEG1000 (1 g PEG1000 (Sigma) dissolved in . . .

DETDESC:

DETD (45)

The . . . or L-leucine) containing 100 .mu.g of tetracycline/mL. The growth obtained after two days is then processed for isolation of plasmid DNA as previously described except that all volumes employed are four times that of the previous example. The final DNA precipitate is dissolved in 1 mL TE.

DETDESC:

DETD (46)

A 10 .mu.L portion of the plasmid **DNA** isolated from S. lividans transformant LL535 is subjected to an in vitro packaging reaction and subsequently transduced to E. coli. . . 500 mL portions of 20-10-5 broth containing 100 .mu.g of amplicillin/mL. After incubation at 30.degree. C., 200 rpm overnight plasmid **DNA** is isolated again as previously described. The isolated plasmid is designated LP.sup.2 127; the estimated size of the plasmid is . .

DETDESC:

DETD (47)

A . . . the vector portion, such as EcoRI, EcoRV or HindIII. Restriction endonuclease digestions are performed by combining 1-2 .mu.g of plasmid DNA 4 .mu.l of a 10.times. solution of salts that are

optimal for the restriction endonuclease being employed and approximately 5-40. .

DETDESC:

DETD (48)

Digestion . . . of LP.sup.2 127 is shown in FIG. 2. A more detailed restriction endonuclease map for the 31.9kb at S. aureofaciens **DNA** cloned in LP.sup.2 127 is shown in FIG. 3.

DETDESC:

DETD (51)

The . . . containing 10 .mu.g of thiostrepton/mL and 100 .mu.g of tetracycline/mL. After five days incubation at 28.degree. C., 200 rpm, plasmid DNA is prepared by a minipreparation procedure, which is similar to previously described plasmid isolation procedures up to the isopropanol precipitation. . . the nucleic acid pellet is dissolved in 1 mL TE and extracted with an equal volume of chlorpane (500 g phenol and 0.5 g 8-hydroxyquinoline equilibrated in a buffer containing 100 mM NaCl, 1 mM EDTA pH8, 10 mM sodium acetate pH 6, plus 500. . .

DETDESC:

DETD (59)

A . . . produce CTC and TC on agar and in broth fermentation, whereas S. lividans containing a plasmid cloning vector without inserted **DNA** does not yield a tetracycline antibiotic. LP.sup.2 128 transformed into S. lividans directs the synthesis of an antiobiotic with acitivity. . .

DETDESC:

DETD (63)

The . . . LL531 are grown on Bennetts agar containing 25 .mu.g of thiostrepton/mL; S. aureofaciens ATCC 13899, the source of the cloned DNA in LP.sup.2 2127 and LP.sup.2 128, is plated on Bennetts agar without drug. After five days of growth at 30.degree. . .

DETDESC:

DETD (66)

Thiostrepton-resistant . . . whereas LP.sup.2 63 transformants do not, thereby indicating that the ability to produce antibiotic is associated with the S. aureofaciens **DNA** present in LP.sup.2 127 and LP.sup.2 128.

DETDESC:

DETD (72)

3. Bibb M. J., J. M. Ward, and D. A. Hopwood. 1978. Transformation of plasmid **DNA** into Streptomyces protoplasts at high frequency. Nature (London) 274:398-400.

DETDESC:

DETD (77)

7. . . . H. -F. Lin, C. L. Kuo. H. -L. Tsai and J. F. -Y. Tsai. 1988. Cloning and expression of a **DNA** sequence conferring cephamycin C production. Bio/Technology 6:1222-1224.

DETDESC:

. . . .

DETD(85)

15. Hohn, B. and J. Collins. A small cosmid for efficient cloning of large **DNA** fragments. Gene 11:291-298.

DETDESC:

DETD(92)

22. Larson, J. L. and C. L. Hershberger. 1986. The minimal replicon of a streptomycete plasmid produces ultrahigh level of plasmid **DNA**. Plasmid 15:199-209.

DETDESC:

DETD(101)

31. . . . F., A. R. Coulson, G. F. Hong, D. F. Hill and G. B. Peterson. 1982. Nucleotide sequence of bacteriophage lambda DNA. J. Mol. Biol. 162:729-773.

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